JUN 1 2000

NDA 20-626/S-001 & S-002

Glaxo Wellcome Inc.
Attention: Ms. Judith Babo
Five Moore Drive
PG Box 13398
Research Triangle Park, NC 27709

Dear Ms. Babo:

Please refer to your supplemental new drug application dated December 18, 1998 and received December 21, 1998 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Imitrex (sumatriptan) Nasal Spray (NDA 20-626/S-002).

We acknowledge receipt of your submission dated August 10, 1998 (NDA 20-626/S-001).

These supplemental new drug applications provide for changes in the labeling in response to events reported during post-marketing surveillance (S-002) and changes to strengthen dosage and administration instructions (S-001).

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

Finally, please note that we have reviewed the content and format of your supplement dated August 10, 1998, providing for changes in the labeling to strengthen the dosage and administration instructions. This supplemental application has been superceded by the labeling approved effective the date of this letter. and will be retained in our files.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted December 18, 1998. S-002). These revisions are terms of the approval of these applications.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated “FPL for approved supplement NDA 20-626/S-002." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please note, if you choose to use a proprietary name for these products, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81:

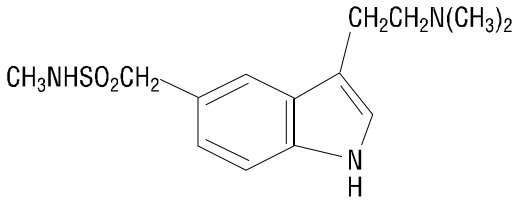
If you have any questions, call Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-5529.

Sincerely,

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

IMITREX®
(sumatriptan)
Nasal Spray

DESCRIPTION: IMITREX (sumatriptan) Nasal Spray contains sumatriptan, a selective 5-hydroxytryptamine$_1$ receptor subtype agonist. Sumatriptan is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-1H-indole-5-methanesulfonamide, and it has the following structure:



The empirical formula is $C_{14}H_{21}N_3O_2S$, representing a molecular weight of 295.4. Sumatriptan is a white to off-white powder that is readily soluble in water and in saline. Each IMITREX Nasal Spray contains 5 or 20 mg of sumatriptan in a 100-µL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg IMITREX Nasal Spray, respectively.

CLINICAL PHARMACOLOGY:

Mechanism of Action: Sumatriptan is an agonist for a vascular 5-hydroxytryptamine$_1$ receptor subtype (probably a member of the 5-HT$_{1D}$ family) having only a weak affinity for 5-HT$_{1A}$, 5-HT$_{5A}$, and 5-HT$_7$ receptors and no significant affinity (as measured using standard radioligand binding assays) or pharmacological activity at 5-HT$_2$, 5-HT$_3$, or 5-HT$_4$ receptor subtypes or at alpha$_1$-, alpha$_2$-, or beta-adrenergic; dopamine$_1$; dopamine$_2$; muscarinic; or benzodiazepine receptors.

The vascular 5-HT$_1$ receptor subtype that sumatriptan activates is present on cranial arteries in both dog and primate, on the human basilar artery, and in the vasculature of human dura mater and mediates vasoconstriction. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that sumatriptan also activates 5-HT$_1$ receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels. Such an action may contribute to the antimigrainous effect of sumatriptan in humans.

In the anesthetized dog, sumatriptan selectively reduces the carotid arterial blood flow with little or no effect on arterial blood pressure or total peripheral resistance. In the cat, sumatriptan selectively constricts the carotid arteriovenous anastomoses while having little effect on blood flow or resistance in cerebral or extracerebral tissues.

Pharmacokinetics: In a study of 20 female volunteers, the mean maximum concentration following a 5- and 20-mg intranasal dose was 5 and 16 ng/mL, respectively. The mean C_{max} following a 6-mg subcutaneous injection is 71 ng/mL (range, 49 to 110 ng/mL). The mean C_{max} is 18 ng/mL (range, 7 to 47 ng/mL) following oral dosing with 25 mg and 51 ng/mL (range, 28 to 100 ng/mL) following oral dosing with 100 mg of sumatriptan. In a study of 24 male volunteers, the bioavailability relative to subcutaneous injection was low, approximately 17%, primarily due to presystemic metabolism and partly due to incomplete absorption.

Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated, but would be expected to be minor, given the low rate of protein binding. The mean volume of distribution after subcutaneous dosing is 2.7 L/kg and the total plasma clearance is approximately 1200 mL/min.

The elimination half-life of sumatriptan administered as a nasal spray is approximately 2 hours, similar to the half-life seen after subcutaneous injection. Only 3% of the dose is excreted in the urine as unchanged sumatriptan; 42% of the dose is excreted as the major metabolite, the indole acetic acid analogue of sumatriptan.

Clinical and pharmacokinetic data indicate that administration of two 5-mg doses, 1 dose in each nostril, is equivalent to administration of a single 10-mg dose in 1 nostril.

Special Populations: ***Renal Impairment:*** The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined, but little clinical effect would be expected as sumatriptan is largely metabolized to an inactive substance.

Hepatic Impairment: The effect of hepatic disease on the pharmacokinetics of subcutaneously and orally administered sumatriptan has been evaluated, but the intranasal dosage form has not been studied in hepatic impairment. There were no statistically significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in hepatically impaired patients compared to healthy controls. However, the liver plays an important role in the presystemic clearance of orally administered sumatriptan. In 1 small study involving oral sumatriptan in hepatically impaired patients (n = 8) matched for sex, age, and weight with healthy subjects, the hepatically impaired patients had an approximately 70% increase in AUC and C_{max} and a t_{max} 40 minutes earlier compared to the healthy subjects. The bioavailability of nasally absorbed sumatriptan following intranasal administration, which would not undergo first-pass metabolism, should not be altered in hepatically impaired patients. The bioavailability of the swallowed portion of the intranasal sumatriptan dose has not been determined, but would be increased in these patients. The swallowed intranasal dose is small, however, compared to the usual oral dose, so that its impact should be minimal.

Age: The pharmacokinetics of oral sumatriptan in the elderly (mean age; 72 years, 2 males and 4 females) and in patients with migraine (mean age; 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age, 30 years). Intranasal sumatriptan has not been evaluated for age differences (see PRECAUTIONS: Geriatric Use).

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects. Intranasal sumatriptan has not been evaluated for race differences.

Drug Interactions: ***Monoamine Oxidase Inhibitors (MAOIs):*** Treatment with MAOIs generally leads to an increase of sumatriptan plasma levels (see CONTRAINDICATIONS and PRECAUTIONS).

MAOI interaction studies have not been performed with intranasal sumatriptan. Due to gut and hepatic metabolic first-pass effects, the increase of systemic exposure after coadministration of an MAO-A inhibitor with oral sumatriptan is greater than after coadministration of the MAOI with subcutaneous sumatriptan. The effects of an MAOI on systemic exposure after intranasal sumatriptan would be expected to be greater than the effect after subcutaneous sumatriptan but smaller than the effect after oral sumatriptan because only swallowed drug would be subject to first-pass effects.

In a study of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of subcutaneous sumatriptan. Under the conditions of this experiment, the result was a 2-fold increase in the area under the sumatriptan plasma concentration x time curve (AUC), corresponding to a 40% increase in elimination half-life. This interaction was not evident with an MAO-B inhibitor.

A small study evaluating the effect of pretreatment with an MAO-A inhibitor on the bioavailability from a 25-mg oral sumatriptan tablet resulted in an approximately 7-fold increase in systemic exposure.

Xylometazoline: An in vivo drug interaction study indicated that 3 drops of xylometazoline (0.1% w/v), a decongestant, administered 15 minutes prior to a 20-mg nasal dose of sumatriptan did not alter the pharmacokinetics of sumatriptan.

CLINICAL TRIALS: The efficacy of IMITREX Nasal Spray in the acute treatment of migraine headaches was demonstrated in 8, randomized, double-blind, placebo-controlled studies, of which 5 used the recommended dosing regimen and used the marketed formulation. Patients enrolled in these 5 studies were predominately female (86%) and Caucasian (95%), with a mean age of 41 (range of 18 to 65). Patients were instructed to treat a moderate to severe headache. Headache response, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of response was assessed for up to 24 hours postdose. A second dose of IMITREX Nasal Spray or other medication was allowed 2 to 24 hours after the initial treatment for recurrent headache. The frequency and time to use of these additional treatments were also determined. In all studies, doses of 10 and 20 mg were compared to placebo in the treatment of 1 to 3 migraine attacks. Patients received doses as a single spray into 1 nostril. In 2 studies, a 5-mg dose was also evaluated.

In all 5 trials utilizing the market formulation and recommended dosage regimen, the percentage of patients achieving headache response 2 hours after treatment was significantly greater among patients receiving IMITREX Nasal Spray at all doses (with one exception) compared to those who received placebo. In 4 of the 5 studies, there was a statistically significant greater percentage of patients with headache response at 2 hours in the 20-mg group when compared to the lower dose groups (5 and 10 mg). There were no statistically significant differences between the 5- and 10-mg dose groups in any study. The results from the 5 controlled clinical trials are summarized in Table 1. Note that, in general, comparisons of results obtained in studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

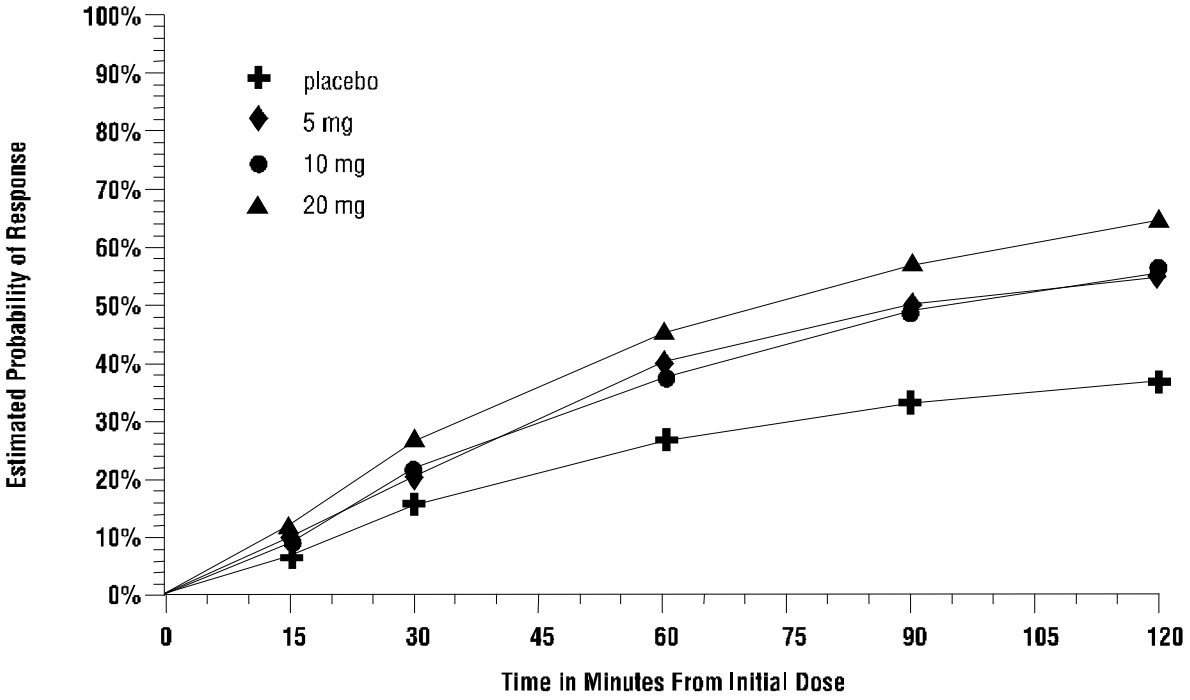
Table 1: Percentage of Patients With Headache Response (No or Mild Pain) 2 Hours Following Treatment

	Placebo	IMITREX Nasal Spray 5 mg	IMITREX Nasal Spray 10 mg	IMITREX Nasal Spray 20 mg
Study 1	25% (n = 63)	49%* (n = 121)	46%* (n = 112)	64%*†‡ (n = 118)
Study 2	25% (n = 138)	Not applicable	44%* (n = 273)	55%*† (n = 277)
Study 3	35% (n = 100)	Not applicable	54%* (n = 106)	63%* (n = 202)
Study 4	29% (n = 112)	Not applicable	43% (n = 106)	62%*† (n = 215)
Study 5§	36% (n = 198)	45%* (n = 296)	53%* (n = 291)	60%*‡ (n = 286)

**P*<0.05 in comparison with placebo.
†*P*<0.05 in comparison with 10 mg.
‡*P*<0.05 in comparison with 5 mg.
§Data are for attack 1 only of multiattack study for comparison.

The estimated probability of achieving an initial headache response over the 2 hours following treatment is depicted in Figure 1.

Figure 1: Estimated Probability of Achieving Initial Headache Response Within 120 Minutes*

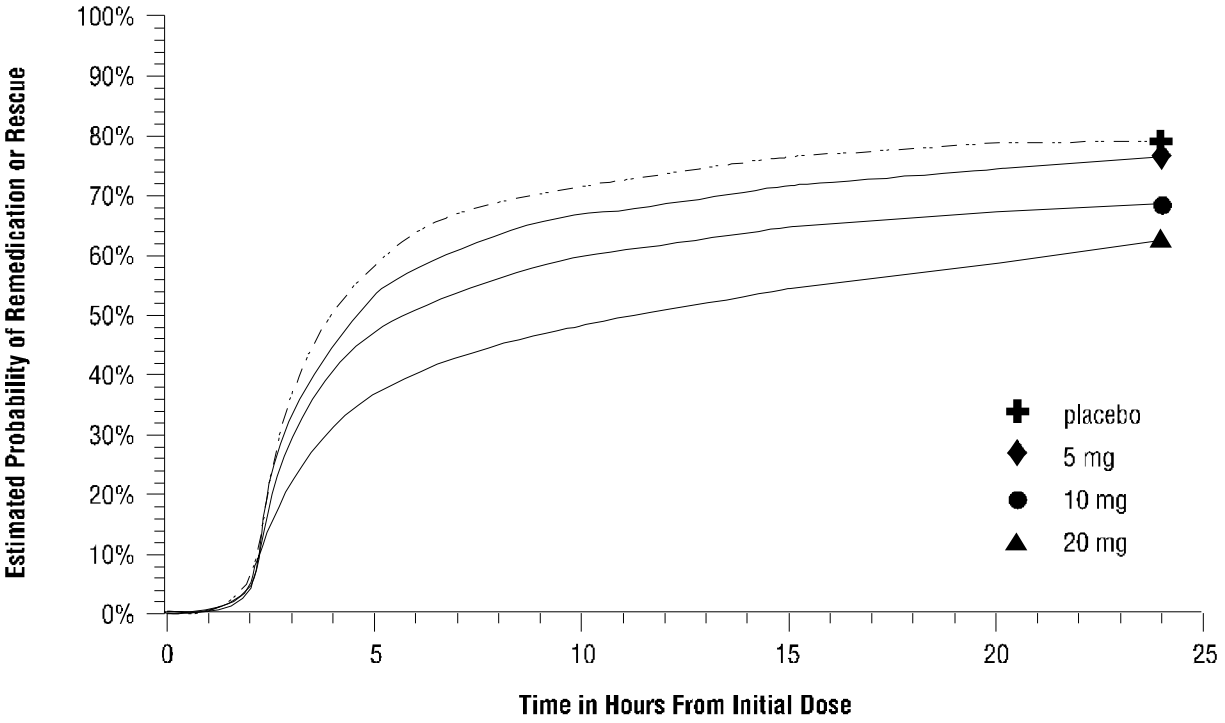


* The figure shows the probability over time of obtaining headache response (no or mild pain) following treatment with intranasal sumatriptan. The averages displayed are based on pooled data from the 5 clinical controlled trials providing evidence of efficacy. Kaplan-Meier plot with patients not achieving response within 120 minutes censored to 120 minutes.

For patients with migraine-associated nausea, photophobia, and phonophobia at baseline, there was a lower incidence of these symptoms at 2 hours following administration of IMITREX Nasal Spray compared to placebo.

Two to 24 hours following the initial dose of study treatment, patients were allowed to use additional treatment for pain relief in the form of a second dose of study treatment or other medication. The estimated probability of patients taking a second dose or other medication for migraine over the 24 hours following the initial dose of study treatment is summarized in Figure 2.

Figure 2: The Estimated Probability of Patients Taking a Second Dose or Other Medication for Migraine Over the 24 Hours Following the Initial Dose of Study Treatment*



* Kaplan-Meier plot based on data obtained in the 3 clinical controlled trials providing evidence of efficacy with patients not using additional treatments censored to 24 hours. Plot also includes patients who had no response to the initial dose. No remedication was allowed within 2 hours postdose.

There is evidence that doses above 20 mg do not provide a greater effect than 20 mg. There was no evidence to suggest that treatment with sumatriptan was associated with an increase in the severity of recurrent headaches. The efficacy of IMITREX Nasal Spray was unaffected by presence of aura; duration of headache prior to treatment; gender, age, or weight of the patient; or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants). There were insufficient data to assess the impact of race on efficacy.

INDICATIONS AND USAGE: IMITREX Nasal Spray is indicated for the acute treatment of migraine attacks with or without aura in adults.

IMITREX Nasal Spray is not intended for the prophylactic therapy of migraine or for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS). Safety and effectiveness of IMITREX Nasal Spray have not been established for cluster headache, which is present in an older, predominantly male population.

CONTRAINDICATIONS: IMITREX Nasal Spray should not be given to patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes. In addition, patients with other significant underlying cardiovascular diseases should not receive IMITREX Nasal Spray. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal

variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease (see WARNINGS).

Because IMITREX Nasal Spray may increase blood pressure, it should not be given to patients with uncontrolled hypertension.

Concurrent administration of MAO-A inhibitors or use within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions).

IMITREX Nasal Spray and any ergotamine-containing or ergot-type medication (like dihydroergotamine or methysergide) should not be used within 24 hours of each other, nor should IMITREX Nasal Spray and another 5-HT_1 agonist.

IMITREX Nasal Spray should not be administered to patients with hemiplegic or basilar migraine.

IMITREX Nasal Spray is contraindicated in patients with hypersensitivity to sumatriptan or any of its components.

IMITREX Nasal Spray is contraindicated in patients with severe hepatic impairment.

WARNINGS: IMITREX Nasal Spray should only be used where a clear diagnosis of migraine headache has been established.

Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: Sumatriptan should not be given to patients with documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that sumatriptan not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, or male over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is modest, at best. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, sumatriptan should not be administered (see CONTRAINDICATIONS).

For patients with risk factors predictive of CAD, who are determined to have a satisfactory cardiovascular evaluation, it is strongly recommended that administration of the first dose of sumatriptan nasal spray take place in the setting of a physician's office or similar medically staffed and equipped facility unless the patient has previously received sumatriptan. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining on the first occasion of use an electrocardiogram (ECG) during the interval immediately following IMITREX Nasal Spray, in these patients with risk factors.

It is recommended that patients who are intermittent long-term users of sumatriptan and who have or acquire risk factors predictive of CAD, as described above, undergo periodic interval cardiovascular evaluation as they continue to use sumatriptan.

The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to sumatriptan.

Drug-Associated Cardiac Events and Fatalities: Serious adverse cardiac events, including acute myocardial infarction, life-threatening disturbances of cardiac rhythm, and death have been reported within

a few hours following the administration of IMITREX® (sumatriptan succinate) Injection or IMITREX® (sumatriptan succinate) Tablets. Considering the extent of use of sumatriptan in patients with migraine, the incidence of these events is extremely low.

The fact that sumatriptan can cause coronary vasospasm, that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to sumatriptan use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.

Premarketing Experience With Sumatriptan: Among approximately 4000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of sumatriptan nasal spray, 1 patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.

Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral sumatriptan, 2 experienced clinical adverse events shortly after receiving oral sumatriptan that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.

Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous sumatriptan, there were 8 patients who sustained clinical events during or shortly after receiving sumatriptan that may have reflected coronary artery vasospasm. Six of these 8 patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these 8 patients, 4 had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.

Postmarketing Experience With Sumatriptan: Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX Injection or IMITREX Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by sumatriptan or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX.

Cardiac events that have been observed to have onset within 1 hour of sumatriptan administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.

Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among domestic reports of serious cardiac events within 1 hour of sumatriptan administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).

Drug-Associated Cerebrovascular Events and Fatalities: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous sumatriptan, and some have resulted in fatalities. The relationship of sumatriptan to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary, sumatriptan having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, care should be taken to exclude other potentially serious neurological conditions. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., cerebrovascular accident, transient ischemic attack).

Other Vasospasm-Related Events: Sumatriptan may cause vasospastic reactions other than coronary artery vasospasm. Both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea have been reported.

Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. Sumatriptan is contraindicated in patients with uncontrolled hypertension (see CONTRAINDICATIONS). Sumatriptan should be administered with caution to patients with controlled hypertension as transient increases in blood pressure and peripheral vascular resistance have been observed in a small proportion of patients.

Local Irritation: Of the 3378 patients using the nasal spray (5-, 10-, or 20-mg doses) on 1 or 2 occasions in controlled clinical studies, approximately 5% noted irritation in the nose and throat. Irritative symptoms such as burning, numbness, paresthesia, discharge, and pain or soreness were noted to be severe in about 1% of patients treated. The symptoms were transient and in approximately 60% of the cases, the symptoms resolved in less than 2 hours. Limited examinations of the nose and throat did not reveal any clinically noticeable injury in these patients. The consequences of extended and repeated use of IMITREX Nasal Spray on the nasal and/or respiratory mucosa have not been systematically evaluated in patients.

No increase in the incidence of local irritation was observed in patients using IMITREX Nasal Spray repeatedly for up to 1 year.

In inhalation studies in rats dosed daily for up to 1 month at exposures as low as one half the maximum daily human exposure (based on dose per surface area of nasal cavity), epithelial hyperplasia (with and without keratinization) and squamous metaplasia were observed in the larynx at all doses tested. These changes were partially reversible after a 2-week drug-free period. When dogs were dosed daily with various formulations by intranasal instillation for up to 13 weeks at exposures of 2 to 4 times the maximum daily human exposure (based on dose per surface area of nasal cavity), respiratory and nasal mucosa exhibited evidence of epithelial hyperplasia, focal squamous metaplasia, granulomata, bronchitis, and fibrosing alveolitis. A no-effect dose was not established. The changes observed in both species are not considered to be signs of either preneoplastic or neoplastic transformation.

Local effects on nasal and respiratory tissues after chronic intranasal dosing in animals have not been studied.

Concomitant Drug Use: In patients taking MAO-A inhibitors, sumatriptan plasma levels attained after treatment with recommended doses are 2-fold (following subcutaneous administration) to 7-fold (following oral administration) higher than those obtained under other conditions. Accordingly, the coadministration of IMITREX Nasal Spray and an MAO-A inhibitor is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Hypersensitivity: Hypersensitivity (anaphylaxis/anaphylactoid) reactions have occurred on rare occasions in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS).

PRECAUTIONS:

General: Chest discomfort and jaw or neck tightness have been reported infrequently following the administration of IMITREX Nasal Spray and have also been reported following use of IMITREX Tablets. Chest, jaw, or neck tightness is relatively common after administration of IMITREX Injection. Only rarely have these symptoms been associated with ischemic ECG changes. However, because sumatriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following sumatriptan should be evaluated for the presence of CAD or a predisposition to Prinzmetal variant angina before receiving additional doses of sumatriptan, and should be monitored electrocardiographically if

dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud syndrome following sumatriptan should be evaluated for atherosclerosis or predisposition to vasospasm (see WARNINGS).

IMITREX Nasal Spray should also be administered with caution to patients with diseases that may alter the absorption, metabolism, or excretion of drugs, such as impaired hepatic or renal function.

There have been rare reports of seizure following administration of sumatriptan. Sumatriptan should be used with caution in patients with a history of epilepsy or structural brain lesions that lower their seizure threshold.

Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received sumatriptan for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion (see WARNINGS).

For a given attack, if a patient does not respond to the first dose of sumatriptan, the diagnosis of migraine headache should be reconsidered before administration of a second dose.

Binding to Melanin-Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Comparable studies were not performed by the intranasal route. Because there could be an accumulation in melanin-rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic effects.

Corneal Opacities: Sumatriptan causes corneal opacities and defects in the corneal epithelium in dogs; this raises the possibility that these changes may occur in humans. While patients were not systematically evaluated for these changes in clinical trials, and no specific recommendations for monitoring are being offered, prescribers should be aware of the possibility of these changes (see ANIMAL TOXICOLOGY).

Information for Patients: See PATIENT INFORMATION at the end of this labeling for the text of the separate leaflet provided for patients.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with sumatriptan.

Drug Interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan within 24 hours of each other should be avoided (see CONTRAINDICATIONS).

MAO-A inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX Nasal Spray in patients receiving MAO-A inhibitors is contraindicated (see CLINICAL PHARMACOLOGY and CONTRAINDICATIONS).

Selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline) have been reported, rarely, to cause weakness, hyperreflexia, and incoordination when coadministered with sumatriptan. If concomitant treatment with sumatriptan and an SSRI is clinically warranted, appropriate observation of the patient is advised.

Drug/Laboratory Test Interactions: IMITREX Nasal Spray is not known to interfere with commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage (rats, 104 weeks) or drinking water (mice, 78 weeks). Average exposures achieved in mice receiving the highest dose (target dose of 160 mg/kg per day) were approximately 184 times the exposure attained in humans after the maximum recommended single intranasal dose of 20 mg. The highest dose administered to rats (160 mg/kg per day, reduced from 360 mg/kg per day during week 21) was approximately 78 times the maximum recommended single intranasal dose of 20 mg on a mg/m^2 basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration. Local effects on nasal and respiratory tissue after chronic intranasal dosing in animals have not been evaluated (see WARNINGS).

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the in vitro mammalian Chinese hamster V79/HGPRT assay). In 2 cytogenetics assays (the in vitro human lymphocyte assay and the in vivo rat micronucleus assay) sumatriptan was not associated with clastogenic activity.

Impairment of Fertility: In a study in which male and female rats were dosed daily with oral sumatriptan prior to and throughout the mating period, there was a treatment-related decrease in fertility secondary to a decrease in mating in animals treated with 50 and 500 mg/kg per day. The highest no-effect dose for this finding was 5 mg/kg per day, or approximately twice the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. It is not clear whether the problem is associated with treatment of the males or females or both combined. In a similar study by the subcutaneous route there was no evidence of impaired fertility at 60 mg/kg per day, the maximum dose tested, which is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis. Fertility studies, in which sumatriptan was administered by the intranasal route, were not conducted.

Pregnancy: Pregnancy Category C. In reproductive toxicity studies in rats and rabbits, oral treatment with sumatriptan was associated with embryolethality, fetal abnormalities, and pup mortality. When administered by the intravenous route to rabbits, sumatriptan has been shown to be embryolethal. Reproductive toxicity studies for sumatriptan by the intranasal route have not been conducted.

There are no adequate and well-controlled studies in pregnant women. Therefore, IMITREX Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In assessing this information, the following findings should be considered.

Embryolethality: When given orally or intravenously to pregnant rabbits daily throughout the period of organogenesis, sumatriptan caused embryolethality at doses at or close to those producing maternal toxicity. In the oral studies this dose was 100 mg/kg per day, and in the intravenous studies this dose was 2.0 mg/kg per day. The mechanism of the embryolethality is not known. The highest no-effect dose for embryolethality by the oral route was 50 mg/kg per day, which is approximately 48 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. By the intravenous route, the highest no-effect dose was 0.75 mg/kg per day, or approximately 0.7 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

The intravenous administration of sumatriptan to pregnant rats throughout organogenesis at 12.5 mg/kg per day, the maximum dose tested, did not cause embryolethality. This dose is approximately 6 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Additionally, in a study in rats given subcutaneous sumatriptan daily, prior to and throughout pregnancy, at 60 mg/kg per day, the maximum dose tested, there was no evidence of increased embryo/fetal lethality. This dose is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Teratogenicity: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in an increased incidence of blood vessel abnormalities (cervicothoracic and umbilical) at doses of

approximately 250 mg/kg per day or higher. The highest no-effect dose was approximately 60 mg/kg per day, which is approximately 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. Oral treatment of pregnant rabbits with sumatriptan during the period of organogenesis resulted in an increased incidence of cervicothoracic vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg per day, or approximately 14 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

A study in which rats were dosed daily with oral sumatriptan prior to and throughout gestation demonstrated embryo/fetal toxicity (decreased body weight, decreased ossification, increased incidence of rib variations) and an increased incidence of a syndrome of malformations (short tail/short body and vertebral disorganization) at 500 mg/kg per day. The highest no-effect dose was 50 mg/kg per day, or approximately 24 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a study in rats dosed daily with subcutaneous sumatriptan prior to and throughout pregnancy, at a dose of 60 mg/kg per day, the maximum dose tested, there was no evidence of teratogenicity. This dose is equivalent to approximately 29 times the maximum recommended single human intranasal dose of 20 mg on a mg/m^2 basis.

Pup Deaths: Oral treatment of pregnant rats with sumatriptan during the period of organogenesis resulted in a decrease in pup survival between birth and postnatal day 4 at doses of approximately 250 mg/kg per day or higher. The highest no-effect dose for this effect was approximately 60 mg/kg per day, or 29 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

Oral treatment of pregnant rats with sumatriptan from gestational day 17 through postnatal day 21 demonstrated a decrease in pup survival measured at postnatal days 2, 4, and 20 at the dose of 1000 mg/kg per day. The highest no-effect dose for this finding was 100 mg/kg per day, approximately 49 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis. In a similar study in rats by the subcutaneous route there was no increase in pup death at 81 mg/kg per day, the highest dose tested, which is equivalent to 40 times the maximum single recommended human intranasal dose of 20 mg on a mg/m^2 basis.

To monitor fetal outcomes of pregnant women exposed to IMITREX, Glaxo Wellcome Inc. maintains a Sumatriptan Pregnancy Registry. Physicians are encouraged to register patients by calling (800) 336-2176.

Nursing Mothers: Sumatriptan is excreted in human breast milk. Therefore, caution should be exercised when considering the administration of IMITREX Nasal Spray to a nursing woman.

Pediatric Use: Safety and effectiveness of IMITREX Nasal Spray in pediatric patients have not been established.

Completed placebo-controlled clinical trials evaluating oral sumatriptan (25 to 100 mg) in pediatric patients aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These studies did not establish the efficacy of oral sumatriptan compared to placebo in the treatment of migraine in adolescents. Adverse events observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse events in these patients appeared to be both dose- and age-dependent, with younger patients reporting events more commonly than older adolescents. Postmarketing experience includes a limited number of reports that describe pediatric patients who have experienced adverse events, some clinically serious, after use of subcutaneous sumatriptan and/or oral sumatriptan. These reports include events similar in nature to those reported rarely in adults. A myocardial infarct has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse events in pediatric patients who might receive injectable, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients aged younger than 18 years is not recommended.

Geriatric Use: The use of sumatriptan in elderly patients is not recommended because elderly patients are more likely to have decreased hepatic function, they are at higher risk for CAD, and blood pressure increases may be more pronounced in the elderly (see WARNINGS).

ADVERSE REACTIONS: Serious cardiac events, including some that have been fatal, have occurred following the use of IMITREX Injection or Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS)**.**

Significant hypertensive episodes, including hypertensive crises, have been reported on rare occasions in patients with or without a history of hypertension (see WARNINGS).

Incidence in Controlled Clinical Trials: Among 3653 patients treated with IMITREX Nasal Spray in active- and placebo-controlled clinical trials, less than 0.4% of patients withdrew for reasons related to adverse events. Table 2 lists adverse events that occurred in worldwide placebo-controlled clinical trials in 3419 migraineurs. The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ.

Only events that occurred at a frequency of 1% or more in the IMITREX Nasal Spray 20-mg treatment group and were more frequent in that group than in the placebo group are included in Table 2.

Table 2: Treatment-Emergent Adverse Events Reported by at Least 1% of Patients in Controlled Migraine Trials

	Percent of Patients Reporting			
Adverse Event Type	Placebo (n = 704)	IMITREX 5 mg (n = 496)	IMITREX 10 mg (n = 1007)	IMITREX 20 mg (n = 1212)
Atypical sensations				
Burning sensation	0.1%	0.4%	0.6%	1.4%
Ear, nose, and throat				
Disorder/discomfort of nasal cavity/sinuses	2.4%	2.8%	2.5%	3.8%
Throat discomfort	0.9%	0.8%	1.8%	2.4%
Gastrointestinal				
Nausea and/or vomiting	11.3%	12.2%	11.0%	13.5%
Neurological				
Bad/unusual taste	1.7%	13.5%	19.3%	24.5%
Dizziness/vertigo	0.9%	1.0%	1.7%	1.4%

Phonophobia also occurred in more than 1% of patients but was more frequent on placebo.

IMITREX Nasal Spray is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-lasting effects. The incidence of adverse events in controlled clinical trials

was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events Observed in Association With the Administration of IMITREX Nasal Spray: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX Nasal Spray in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value of the quantitative frequency estimates provided. Event frequencies are calculated as the number of patients who used IMITREX Nasal Spray (5, 10, or 20 mg in controlled and uncontrolled trials) and reported an event divided by the total number of patients (n = 3711) exposed to IMITREX Nasal Spray. All reported events are included except those already listed in the previous table, those too general to be informative, and those not reasonably associated with the use of the drug. Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1000 patients and rare adverse events are those occurring in fewer than 1/1000 patients.

Atypical Sensations: Infrequent were tingling, warm/hot sensation, numbness, pressure sensation, feeling strange, feeling of heaviness, feeling of tightness, paresthesia, cold sensation, and tight feeling in head. Rare were dysesthesia and prickling sensation.

Cardiovascular: Infrequent were flushing and hypertension (see WARNINGS), palpitations, tachycardia, changes in ECG, and arrhythmia (see WARNINGS and PRECAUTIONS). Rare were abdominal aortic aneurysm, hypotension, bradycardia, pallor, and phlebitis.

Chest Symptoms: Infrequent were chest tightness, chest discomfort, and chest pressure/heaviness (see PRECAUTIONS: General).

Ear, Nose, and Throat: Infrequent were disturbance of hearing and ear infection. Rare were otalgia and Meniere disease.

Endocrine and Metabolic: Infrequent was thirst. Rare were galactorrhea, hypothyroidism, and weight loss.

Eye: Infrequent were irritation of eyes and visual disturbance.

Gastrointestinal: Infrequent were abdominal discomfort, diarrhea, dysphagia, and gastroesophageal reflux. Rare were constipation, flatulence/eructation, hematemesis, intestinal obstruction, melena, gastroenteritis, colitis, hemorrhage of gastrointestinal tract, and pancreatitis.

Mouth and Teeth: Infrequent was disorder of mouth and tongue (e.g., burning of tongue, numbness of tongue, dry mouth).

Musculoskeletal: Infrequent were neck pain/stiffness, backache, weakness, joint symptoms, arthritis, and myalgia. Rare were muscle cramps, tetany, intervertebral disc disorder, and muscle stiffness.

Neurological: Infrequent were drowsiness/sedation, anxiety, sleep disturbances, tremors, syncope, shivers, chills, depression, agitation, sensation of lightness, and mental confusion. Rare were difficulty concentrating, hunger, lacrimation, memory disturbances, monoplegia/diplegia, apathy, disturbance of smell, disturbance of emotions, dysarthria, facial pain, intoxication, stress, decreased appetite, difficulty coordinating, euphoria, and neoplasm of pituitary.

Respiratory: Infrequent were dyspnea and lower respiratory tract infection. Rare was asthma.

Skin: Infrequent were rash/skin eruption, pruritus, and erythema. Rare were herpes, swelling of face, sweating, and peeling of skin.

Urogenital: Infrequent were dysuria, disorder of breasts, and dysmenorrhea. Rare were endometriosis and increased urination.

Miscellaneous: Infrequent were cough, edema, and fever. Rare were hypersensitivity, swelling of extremities, voice disturbances, difficulty in walking, and lymphadenopathy.

Other Events Observed in the Clinical Development of IMITREX: The following adverse events occurred in clinical trials with IMITREX Injection and IMITREX Tablets. Because the reports include events observed in open and uncontrolled studies, the role of IMITREX in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Breasts: Breast swelling; cysts, lumps, and masses of breasts; nipple discharge; primary malignant breast neoplasm; and tenderness.

Cardiovascular: Abnormal pulse, angina, atherosclerosis, cerebral ischemia, cerebrovascular lesion, heart block, peripheral cyanosis, pulsating sensations, Raynaud syndrome, thrombosis, transient myocardial ischemia, various transient ECG changes (nonspecific ST or T wave changes, prolongation of PR or QTc intervals, sinus arrhythmia, nonsustained ventricular premature beats, isolated junctional ectopic beats, atrial ectopic beats, delayed activation of the right ventricle), and vasodilation.

Ear, Nose, and Throat: Allergic rhinitis; ear, nose, and throat hemorrhage; external otitis; feeling of fullness in the ear(s); hearing disturbances; hearing loss; nasal inflammation; sensitivity to noise; sinusitis; tinnitus; and upper respiratory inflammation.

Endocrine and Metabolic: Dehydration; endocrine cysts, lumps, and masses; elevated thyrotropin stimulating hormone (TSH) levels; fluid disturbances; hyperglycemia; hypoglycemia; polydipsia; and weight gain.

Eye: Accommodation disorders, blindness and low vision, conjunctivitis, disorders of sclera, external ocular muscle disorders, eye edema and swelling, eye itching, eye hemorrhage, eye pain, keratitis, mydriasis, and vision alterations

Gastrointestinal: Abdominal distention, dental pain, disturbances of liver function tests, dyspeptic symptoms, feelings of gastrointestinal pressure, gallstones, gastric symptoms, gastritis, gastrointestinal pain, hypersalivation, hyposalivation, oral itching and irritation, peptic ulcer, retching, salivary gland swelling, and swallowing disorders.

Hematological Disorders: Anemia.

Injection Site Reaction

Miscellaneous: Contusions, fluid retention, hematoma, hypersensitivity to various agents, jaw discomfort, miscellaneous laboratory abnormalities, overdose, "serotonin agonist effect", and speech disturbance.

Musculoskeletal: Acquired musculoskeletal deformity, arthralgia and articular rheumatitis, muscle atrophy, muscle tiredness, musculoskeletal inflammation, need to flex calf muscles, rigidity, tightness, and various joint disturbances (pain, stiffness, swelling, ache).

Neurological: Aggressiveness, bradylogia, cluster headache, convulsions, detachment, disturbances of taste, drug abuse, dystonia, facial paralysis, globus hystericus, hallucinations, headache, heat sensitivity, hyperesthesia, hysteria, increased alertness, malaise/fatigue, migraine, motor dysfunction, myoclonia, neuralgia, neurotic disorders, paralysis, personality change, phobia, photophobia, psychomotor disorders, radiculopathy, raised intracranial pressure, relaxation, stinging sensations, transient hemiplegia, simultaneous hot and cold sensations, suicide, tickling sensations, twitching, and yawning.

Pain and Other Pressure Sensations: Chest pain, neck tightness/pressure, throat/jaw pain/tightness/pressure, and pain (location specified).

Respiratory: Breathing disorders, bronchitis, diseases of the lower respiratory tract, hiccoughs, and influenza.

Skin: Dry/scaly skin, eczema, seborrheic dermatitis, skin nodules, skin tenderness, tightness of skin, and wrinkling of skin.

Urogenital: Abortion, abnormal menstrual cycle, bladder inflammation, hematuria, inflammation of fallopian tubes, intermenstrual bleeding, menstruation symptoms, micturition disorders, renal calculus, urethritis, urinary frequency, and urinary infections.

Postmarketing Experience (Reports for Subcutaneous or Oral Sumatriptan): The following section enumerates potentially important adverse events that have occurred in clinical practice and that have been reported spontaneously to various surveillance systems. The events enumerated represent reports arising from both domestic and nondomestic use of oral or subcutaneous dosage forms of sumatriptan. The events enumerated include all except those already listed in the ADVERSE REACTIONS section above or those too general to be informative. Because the reports cite events reported spontaneously from worldwide postmarketing experience, frequency of events and the role of sumatriptan in their causation cannot be reliably determined. It is assumed, however, that systemic reactions following sumatriptan use are likely to be similar regardless of route of administration.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Cardiovascular: Atrial fibrillation, cardiomyopathy, colonic ischemia (see WARNINGS), Prinzmetal variant angina, pulmonary embolism, shock, thrombophlebitis.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis.

Gastrointestinal: Ischemic colitis with rectal bleeding (see WARNINGS), xerostomia.

Hepatic: Elevated liver function tests.

Neurological: Central nervous system vasculitis, cerebrovascular accident, dysphasia, subarachnoid hemorrhage.

Non-Site Specific: Angioneurotic edema, cyanosis, death (see WARNINGS), temporal arteritis.

Psychiatry: Panic disorder.

Respiratory: Bronchospasm in patients with and without a history of asthma.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria; in addition, severe anaphylaxis/anaphylactoid reactions have been reported [see WARNINGS]), photosensitivity.

Urogenital: Acute renal failure.

DRUG ABUSE AND DEPENDENCE: One clinical study with IMITREX (sumatriptan succinate) Injection enrolling 12 patients with a history of substance abuse failed to induce subjective behavior and/or physiologic response ordinarily associated with drugs that have an established potential for abuse.

OVERDOSAGE: In clinical trials, the highest single doses of IMITREX Nasal Spray administered without significant adverse effects were 40 mg to 12 volunteers and 40 mg to 85 migraine patients, which is twice the highest single recommended dose. In addition, 12 volunteers were administered a total daily dose of 60 mg (20 mg 3 times daily) for 3.5 days without significant adverse events.

Overdose in animals has been fatal and has been heralded by convulsions, tremor, paralysis, inactivity, ptosis, erythema of the extremities, abnormal respiration, cyanosis, ataxia, mydriasis, salivation, and lacrimation. The elimination half-life of sumatriptan is about 2 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of patients after overdose with IMITREX Nasal Spray should continue for at least 10 hours or while symptoms or signs persist. It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

DOSAGE AND ADMINISTRATION: In controlled clinical trials, single doses of 5, 10, or 20 mg of IMITREX Nasal Spray administered into one nostril were effective for the acute treatment of migraine in adults. A greater proportion of patients had headache response following a 20-mg dose than following a 5- or 10-mg dose (see CLINICAL TRIALS). Individuals may vary in response to doses of IMITREX Nasal Spray. The choice of dose should therefore be made on an individual basis, weighing the possible benefit of the 20-mg dose with the potential for a greater risk of adverse events. A 10-mg dose may be achieved by the administration of a single 5-mg dose in each nostril. There is evidence that doses above 20 mg do not provide a greater effect than 20 mg.

If the headache returns, the dose may be repeated once after 2 hours, not to exceed a total daily dose of 40 mg. The safety of treating an average of more than four headaches in a 30-day period has not been established.

HOW SUPPLIED: IMITREX Nasal Spray 5 mg (NDC 0173-0524-00) and 20 mg (NDC 0173-0523-00) are each supplied in boxes of 6 nasal spray devices. Each unit dose spray supplies 5 and 20 mg, respectively, of sumatriptan.

Store between 36° and 86°F (2° and 30°C). Protect from light.

ANIMAL TOXICOLOGY:

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg per day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60-week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100-mg oral dose or 3 times the human exposure after a 6-mg subcutaneous dose or 22 times the human exposure after a single 20-mg intranasal dose. There is evidence of alterations in corneal appearance on the first day of intranasal dosing to dogs. Changes were noted at the lowest dose tested, which was approximately 2 times the maximum single human intranasal dose of 20 mg on a mg/m^2 basis.

PATIENT INFORMATION: The following wording is contained in a separate leaflet provided for patients.

Information for the Patient
IMITREX® (sumatriptan) Nasal Spray

Please read this leaflet carefully before you administer IMITREX Nasal Spray. This provides a summary of the information available on your medicine. Please do not throw away this leaflet until you have finished your medicine. You may need to read this leaflet again. This leaflet does not contain all the information on IMITREX Nasal Spray. For further information or advice, ask your doctor or pharmacist.

Information About Your Medicine:

The name of your medicine is IMITREX (sumatriptan) Nasal Spray. It can be obtained only by prescription from your doctor. The decision to use IMITREX Nasal Spray is one that you and your doctor should make jointly, taking into account your individual preferences and medical circumstances. If you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40), you should tell your doctor, who should evaluate you for heart disease in order to determine if IMITREX is appropriate for you. Although the vast majority of those who have taken IMITREX have not experienced any significant side effects, some individuals have experienced serious heart problems and, rarely, considering the extensiveness of IMITREX use worldwide, deaths have been reported. In all but a few instances, however,

serious problems occurred in people with known heart disease and it was not clear whether IMITREX was a contributory factor in these deaths.

1. The Purpose of Your Medicine:

IMITREX Nasal Spray is intended to relieve your migraine, but not to prevent or reduce the number of attacks you experience. Use IMITREX Nasal Spray only to treat an actual migraine attack.

2. Important Questions to Consider Before Using IMITREX Nasal Spray:

If the answer to any of the following questions is **YES** or if you do not know the answer, then please discuss it with your doctor before you use IMITREX Nasal Spray.

- Are you pregnant? Do you think you might be pregnant? Are you trying to become pregnant? Are you using inadequate contraception? Are you breastfeeding?
- Do you have any chest pain, heart disease, shortness of breath, or irregular heartbeats? Have you had a heart attack?
- Do you have risk factors for heart disease (such as high blood pressure, high cholesterol, obesity, diabetes, smoking, strong family history of heart disease, or you are postmenopausal or a male over 40)?
- Have you had a stroke, transient ischemic attacks (TIAs), or Raynaud syndrome?
- Do you have high blood pressure?
- Have you ever had to stop taking this or any other medication because of an allergy or other problems?
- Are you taking any other migraine medications, including other 5-HT_1 agonists or any other medications containing ergotamine, dihydroergotamine, or methysergide?
- Are you taking any medication for depression (monoamine oxidase inhibitors or selective serotonin reuptake inhibitors [SSRIs])?
- Have you had, or do you have, any disease of the liver or kidney?
- Have you had, or do you have, epilepsy or seizures?
- Is this headache different from your usual migraine attacks?

Remember, if you answered **YES** to any of the above questions, then discuss it with your doctor.

3. The Use of IMITREX Nasal Spray During Pregnancy:

Do not use IMITREX Nasal Spray if you are pregnant, think you might be pregnant, are trying to become pregnant, or are not using adequate contraception, unless you have discussed this with your doctor.

4. How to Use IMITREX Nasal Spray:

Before using IMITREX Nasal Spray, see the enclosed instruction pamphlet. For adults, the usual dose is a single nasal spray administered into 1 nostril. If your headache comes back, a second nasal spray may be administered anytime after 2 hours of administering the first spray. For any attack where you have no response to the first nasal spray, do not take a second nasal spray without first consulting with your doctor. Do not administer more than a total of 40 mg of IMITREX Nasal Spray in any 24-hour period. The effects of long-term repeated use of IMITREX Nasal Spray on the surfaces of the nose and throat have not been specifically studied. The safety of treating an average of more than 4 headaches in a 30-day period has not been established.

5. Side Effects to Watch for:

- Some patients experience pain or tightness in the chest or throat when using IMITREX Nasal Spray. If this happens to you, then discuss it with your doctor before using any more IMITREX Nasal Spray. If the chest pain is severe or does not go away, call your doctor immediately.
- If you have sudden and/or severe abdominal pain following IMITREX Nasal Spray, call your doctor immediately.

- Shortness of breath; wheeziness; heart throbbing; swelling of eyelids, face, or lips; or a skin rash, skin lumps, or hives happens rarely. If it happens to you, then tell your doctor immediately. Do not take any more IMITREX Nasal Spray unless your doctor tells you to do so.
- Some people may have feelings of tingling, heat, flushing (redness of face lasting a short time), heaviness or pressure after treatment with IMITREX Nasal Spray. A few people may feel drowsy, dizzy, tired, sick, or may experience nasal irritation. Tell your doctor of these symptoms at your next visit.
- If you feel unwell in any other way or have any symptoms that you do not understand, you should contact your doctor immediately.

6. What to Do if an Overdose Is Taken:

If you have taken more medication than you have been told, contact either your doctor, hospital emergency department, or nearest poison control center immediately.

7. Storing Your Medicine:

Keep your medicine in a safe place where children cannot reach it. It may be harmful to children. Store your medication away from heat and light. Do not store at temperatures above 86°F (30°C), or below 36°F (2°C). If your medication has expired (the expiration date is printed on the treatment pack), throw it away as instructed. If your doctor decides to stop your treatment, do not keep any leftover medicine unless your doctor tells you to. Throw away your medicine as instructed.

GlaxoWellcome

Glaxo Wellcome Inc.
Research Triangle Park, NC 27709

US Patent Nos. 4,816,470; 5,037,845; and 5,554,639

December 1998 RL-601